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EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1642

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
10/033,577

Applicant(s)
Vallera et al

Examiner
Karen Canella

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1642



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 months MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above, claim(s) 27-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No: _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4 6) ☐ Other: _____

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DETAILED ACTION

1. Acknowledgment is made of applicant election without traverse of Group I, drawn to a method of killing a tumor cell comprising contacting said cell with a fusion toxin comprising the toxin domain of diphtheria toxin and a urokinase-type plasminogen activator domain, fusion toxins, pharmaceutical compositions thereof. Applicants election of the patentably distinct species of glioblastoma is also acknowledged. It is noted that claim 12 is broader in scope than indicated in the restriction requirement. Thus, Group I is more accurately described as being drawn to methods for killing tumor cells comprising the administration of fusion toxins, wherein said fusion toxin comprises a urokinase-type plasminogen activator domain.

Claims 1-29 are pending. Claims 27-29, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-26 are examined on the merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "pharmaceutical composition" in claim 26 lacks proper antecedent basis in claim 21. For purpose of examination, claim 26 will be read as dependent on claim 25.

Further, it is unclear how the limitation of "an article of manufacture" would further limit the fusion toxin of claim 21 or the pharmaceutical composition of claim 25..

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 12, 13, 15, 17, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Rajagopal et al (Journal of biological Chemistry, 2000, vol. 275, pp. 7566-7573).

Claim 12 is drawn to a method for killing a glioblastoma tumor cell comprising contacting said cell with a fusion toxin comprising a urokinase-type plasminogen activator domain. Claim 13 is drawn in part to the method of claim 12 wherein said fusion toxin comprises a toxin domain of Pseudomonas exotoxin. Claim 15 is drawn in part to the method of claim 12 wherein said fusion toxin comprises an internalization domain of Pseudomonas exotoxin. Claim 17 embodies the method of claim 12 wherein said urokinase-type plasminogen activator domain is capable of binding to a urokinase-type plasminogen activator receptor. Claim 18 embodies the method of claim 17 wherein said urokinase-type plasminogen activator domain comprises the amino terminal fragment of urokinase-type plasminogen activator. Claim 19 specifies that the glioblastoma tumor cells of claim 12 express the urokinase-type-plasminogen activator.

Rajagopal et al disclose a method for killing a glioblastoma tumor cell comprising contacting said cell with a fusion toxins, wherein said toxins comprise the amino terminus of urokinase plasminogen activator (page 7566, column 1, lines 6-9 after the abstract, and figure 1, and page 7569, column 1, lines 4-6 under the heading "Cytotoxicity and specificity of ATF-toxins toward a Variety of Malignant Cells") and domains II, part of domain Ib and domain III of Pseudomonas exotoxin, wherein domain II comprises the translocation domain (Figure 1 and page 7567, lines 15-16). Rajagopal et al disclose that the fusion toxins bind to the urokinase plasminogen receptor (page 7569, first column, lines 16-19 of the first full paragraph and page 7569, second column, under the heading "Binding of ATF-toxins to uPAR") and that said

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glioblastoma cells express the urokinase plasminogen receptor (page 770, first column, lines 6-10 under the heading "comparison of the cytotoxic Activities of ATF-toxins and their surface Expression of uPAR"). Rajagopal et al disclose that the fusion toxins were internalized into cells and that amino acids 280-313 mediate translocation of the toxin into the cytosol and the carboxyl terminal sequences of REDL and KDEL facilitates said translocation (page 7567, column 1, lines 11-27).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 12, 13, 15, 17, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajagopal et al (Journal of Biological Chemistry, 2000, vol. 275, pp. 7566-7573, reference ABB of the IDS filed May 15, 2002) in view of Fabbri et al (FASEB Journal, 1997, Vol. 11, pp. 1169-1176, reference AR of the IDS filed May 15, 2002) and Leppla et al (U.S. 5,591,631) and Wels et al (WO 96/13599) and Arnon (WO 94/26308) and McDonald et al (WO 00/04926) and Morishita et al (Nucleic Acids symposium series, 1996, Vol. 35, pp. 291-

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292) and Pastan et al (Journal of biological chemistry, 1989, Vol. 264, pp. 15157-15160. Reference AAA of the IDS filed May 15, 2002) and Baty et al (Molecular Microbiology, 1988, Vol. 2, pp. 807-811) and el Kouhen et al (European Journal of Biochemistry, 1993, vol. 214, pp. 635-639) and Geoff et al (Protein engineering, 1997, Vol. 10, suppl. page 5) and Bouveret et al (Molecular Microbiology, 1997, vol. 23, pp. 909-920) and Lacy et al (Journal of Molecular Biology, 1999, Vol. 291, pp. 1091-1104) and Wiedlocha et al (Cancer research, 1991, Vol. 51, pp. 916-920) and Olsnes et al (Journal of Biological Chemistry, 1982, Vol. 257, pp. 13263-13270).

The specific embodiments of claims 12 and 17-19 are set forth above. Claim 13 is further drawn to the method of claim 12 wherein said fusion toxin comprises a toxin domain of a toxin selected from the group consisting of colicin, anthrax toxin, tetanus toxin, botulinum toxin, saporin, abrin, bryodin, pokeweed anti-viral protein, viscumin and gelonin. Claim 15 is further drawn to the method of claim 12 wherein said fusion toxin comprises an internalization domain of a toxin selected from the group consisting of colicin, delta-endotoxin, anthrax toxin, tetanus toxin and botulinum toxin.

Rajagopal et al teach a method of killing a glioblastoma cell comprising administering a fusion toxin comprising the internalization domains and toxin domains of Pseudomonas exotoxin and an amino terminal fragment of urokinase plasminogen activator, for the reasons set forth above. Rajagopal et al do not teach a method for killing glioblastoma cells comprising administering fusion toxins comprising the toxin domains of colicin, anthrax, tetanus, botulinum, saporin, abrin, bryodin, poke-weed anti-viral protein, viscumin or gelonin, nor do Rajagopal et al teach a fusion toxin comprising an internalization domain of colicin, delta-endotoxin. Anthrax, tetanus, or botulinum.

Fabbrini et al teach a method of killing cells expressing the urokinase plasminogen activator receptor comprising contacting said cells with a fusion toxin comprising the amino terminal fragment of urokinase plasminogen activator and the toxin domain of saporin (page

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1173, under the heading "Cell killing experiments") Fabbrini et al teach that pro-urokinase was able to inhibit the cytotoxicity of the recombinant saporin fusion protein thus demonstrating that the cytotoxicity of said fusion protein is due to binding to the urokinase plasminogen activator receptor (page 1173, lines 1-8 under the heading "Competition Experiments"). Fabbrini et al teach that the amino terminal fragment of urokinase plasminogen activator is necessary for targeting the receptor of urokinase plasminogen activator, but that internalization at said receptor takes place because of the toxin (page 1175, column 1, lines 1-5, first full paragraph).

Leppla et al (U.S. 5,591,631) teach anthrax-toxin fusion proteins and hybrid toxins and immunotoxins comprising anthrax toxin lethal factor fused to the toxin domain of *Pseudomonas* exotoxin. Leppla et al identify the anthrax toxin lethal factor as the translocation domain of anthrax toxin. One of skill in the art would conclude that the translocation domains are functional outside of the context of the wild type toxin as Leppla et al teach that the hybrid toxin comprising P exotoxin and the anthrax lethal factor increases the toxicity of the P exotoxin by means of increasing translocation of the P exotoxin into the cytosol.

Arnon teaches immunotoxins comprising the toxin domains of botulinum or tetanus toxins.

McDonald et al teach immunotoxins comprising gelonin, saporin, abrin, ricin, colicin and pokeweed anti-viral protein.

Wiedocha et al teach an immunotoxin comprising the toxin domain of mistletoe lectin I. Olsnes et al teach that viscumin is a toxic lectin from mistletoe.

Baty et al and el Kouhen et al and Geoff et al and Bouveret et al teach the translocation domains of colicin A, colicin N, colicin E9, and colicin E3, respectively.

Lacy et al teach the translocation domains of botulinum and tetanus neurotoxins.

Pastan et al teach the translocation domain of *Pseudomonas* exotoxin.

Wels et al teach the translocation domains of colicin A, and d-endotoxin.

Morishita et al teach the translocation domain of ricin.

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the toxin domain of colicin, anthrax, tetanus, botulinum, saporin, abrin, bryodin, pokeweed anti-viral protein, vescumin or gelonin for the toxin domain of Pseudomonas exotoxin in the method of killing glioblastoma cells as taught by Rajagopal et al; it would also be obvious to substitute the translocation domain of colicin, delta-endotoxin, anthrax, botulinum, or tetanus for the translocation domain of P endotoxin in the method of killing glioblastoma cells as taught by Rajagopal et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success

a. by the teachings of Arnon and McDonald et al and Wiedocha et al which identify the toxic domains of botulinum, tetanus, gelonin, saporin, abrin, ricin, colicin, pokeweed anti-viral protein and vscumin;

b. by the teachings of Baty et al and el Kouhen et al and Geoff et al and Bouveret et al and Lacy et al and Pastan et al and Wels et al and Morishita et al which identify the translocation domains for colicins, botulinum, tetanus, P endotoxin and ricin;

c. by the teachings of Fabbrini et al on the contribution of the toxin moiety toward internalization at the urokinase plasminogen activator receptor and the teachings of Rajagopal et al on the importance of facilitating transportation of the toxin domain into the cytosol; and

d. by the teachings of Leppala on the independent functioning of the translocation domain and the toxin domain.

One of skill in the art would recognize by the teachings Leppala et al that the fusion toxin can be effective with any toxin which has be utilized in the art as an immunotoxin and that the translocation domain is synonymous for the internalization domain and that any of the aforesaid translocation domains can be fused to any of the aforesaid toxin domain in a fusion toxin comprising urokinase plasminogen activator to facilitate delivery of a toxin into the cytoplasm of the glioblastoma tumor cell expressing the urokinase plasminogen activator receptor.

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8. Claims 1-5 and 7-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajagopal et al (Journal of biological Chemistry, 2000, vol. 275, pp. 7566-7573) in view of Greenfield et al (Science, 1987, vol. 238, pp. 536-539) and Fabbrini et al (FASEB Journal, 1997, Vol. 11, pp. 1169-1176, reference AR of the IDS filed May 15, 2002).

The specific embodiments of claims 12, 17, 18 and 19 are recited above. Claim 1 is drawn to a method for killing a tumor cell comprising contacting said tumor cell with a fusion toxin comprising the toxin domain of diphtheria toxin and a urokinase-type plasminogen activator domain. Claim 2 embodies the method of claim 1 wherein said tumor cell is a brain tumor cell. Claims 3 and 4 embody the method of claim 2 wherein said brain tumor is selected from the group consisting of glioblastoma. Because of the Requirement of the election of species in Paper No. 5, claims 1-4 will be examined to the extent that they read on glioblastoma. Claim 5 is drawn to the method of claim 1 wherein said tumor cell expresses the urokinase-type plasminogen activator receptor. Claim 7 embodies the method of claim 1 wherein said fusion toxin comprises the translocation enhancer region of diphtheria toxin. Claim 8 embodies the method of claim 1 wherein said fusion toxin comprises the amino terminal 390 amino acids of diphtheria toxin. Claim 9 is drawn to the method of claim 1 wherein said urokinase-type plasminogen activator domain is capable of binding to urokinase-type plasminogen activator receptor. Claim 10 embodies the method of claim 9 wherein said plasminogen activator domain comprises the amino terminal fragment of urokinase type plasminogen activator. Claim 11 embodies the method of claim 1 wherein said fusion toxin comprises the toxin domain of diphtheria toxin, the translocation enhancing region of diphtheria toxin and the amino terminal fragment of urokinase type plasminogen activator. Claim 13 is drawn in part to the method of claim 12 wherein said fusion toxin comprises a toxin domain of diphtheria toxin. Claim 14 embodies the method of claim 12 wherein said fusion toxin comprises the toxin domain of diphtheria toxin. Claim 15 is drawn in part to the method of claim 12 wherein said fusion toxin comprises an internalization domain of diphtheria toxin. Claim 16 embodies the method of claim

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12 wherein said fusion toxin comprises the translocation enhancing region of diphtheria toxin. Claim 20 embodies the method of claim 12 wherein said fusion toxin comprises the toxin domain of diphtheria toxin, the translocation enhancing region of diphtheria toxin, and the amino terminal fragment of the urokinase-type plasminogen activator.

Claim 21 is drawn to a fusion toxin comprising the toxin domain of diphtheria toxin and a urokinase-type plasminogen activator. Claim 22 embodies the fusion toxin of claim 21 wherein said fusion toxin further comprises the translocation enhancing region of diphtheria toxin. Claim 23 embodies the fusion toxin of claim 21 wherein said urokinase-type plasminogen activator domain comprises the amino terminal fragment of urokinase-type plasminogen activator. Claim 24 embodies the fusion toxin of claim 21 wherein said exotoxin comprises the toxin domain of diphtheria toxin, the translocation enhancing region of diphtheria toxin and the amino terminal fragment of urokinase-type plasminogen activator.

Rajagopal et al teach a method of killing a glioblastoma cell comprising administering a fusion toxin comprising the internalization domains and toxin domains of Pseudomonas exotoxin and an amino terminal fragment of urokinase plasminogen activator, for the reasons set forth above. Rajagopal et al do not teach a method for killing glioblastoma cells comprising administering fusion toxins comprising the toxin domain of diphtheria toxin, nor do Rajagopal et al teach a fusion toxin comprising an internalization domain of diphtheria toxin.

Fabbrini et al teach a method of killing cells expressing the urokinase plasminogen activator receptor comprising contacting said cells with a fusion toxin comprising the amino terminal fragment of urokinase plasminogen activator and the toxin domain of saporin (page 1173, under the heading "Cell killing experiments") Fabbrini et al teach that pro-urokinase was able to inhibit the cytotoxicity of the recombinant saporin fusion protein thus demonstrating that the cytotoxicity of said fusion protein is due to binding to the urokinase plasminogen activator receptor (page 1173, lines 1-8 under the heading "Competition Experiments"). Fabbrini et al teach that the amino terminal fragment of urokinase plasminogen activator is necessary for

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targeting the receptor of urokinase plasminogen activator, but that internalization at said receptor takes place because of the toxin (page 1175, column 1, lines 1-5, first full paragraph).

Greenfield et al teach recombinant mutant forms of diphtheria toxin which retain membrane translocation ability but lose the ability to bind to the diphtheria toxin receptor. Greenfield et al teach immunotoxins comprising said mutant diphtheria toxins are much more effective in killing target cells than immunotoxins comprising only the toxin domain of diphtheria toxin. Therefore one of skill in the art would conclude that it is advantageous to include the membrane translocation domain with the toxin domain in a fusion protein to be targeted to a specific cells type.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute a mutant diphtheria toxin lacking the ability to bind to the diphtheria toxin receptor, but maintaining the translocation and toxin domains for the pseudomonas endotoxin in a fusion toxin comprising the amino terminal fragment of urokinase plasminogen activator as taught by Rajagopal et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Fabbrini et al on the toxin mediated cytotoxicity of fusion toxins comprising the amino terminal fragment of urokinase plasminogen activator and saporin and the teaching of Greenfield et al on the mutant diphtheria toxins which are lacking diphtheria toxin receptor binding activity by maintaining the ability to translocate into the cytosol. One of skill in the art would recognize that such a fusion toxin comprising diphtheria toxin would also be effective in a method of killing glioblastoma cells.

9. Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajagopal et al (Journal of biological Chemistry, 2000, vol. 275, pp. 7566-7573) in view of Greenfield et al (Science, 1987, vol. 238, pp. 536-539) and Fabbrini et al (FASEB Journal, 1997, Vol. 11, pp. 1169-1176, reference ARE of the IDS filed May 15, 2002) as applied to claims 1-5, 7-24 and 26

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above, and further in view of Oldfield et al (Current Topics in Microbiology and Immunology, 1998, Vol. 234, pp. 97-114, reference AZ of the IDS filed May 15, 2002) and Mori et al (Journal of Neuro-Oncology, 2000, Vol. 46, pp. 115-123, reference AX of the IDS filed May 15, 2002).

The specific embodiments of claims 1-5 and 7-24 are set forth above. Claim 6 is drawn to the method of claim 1 wherein contacting the tumor cell occurs in vivo. Claim 25 is drawn to a pharmaceutical composition comprising the fusion toxin of claim 21. Claim 26 is drawn to an article of manufacture comprising the pharmaceutical composition of claim 25. The combination of Rajagopal et al and Greenfield et al and Fabbrini et al render obvious claims 1-5 and 7-24 for the reasons set forth above. Neither Rajagopal et al nor Greenfield et al nor Fabbrini et al teach a method wherein the contacting of the tumor cell with the fusion toxin is carried out in vivo.

Oldfield et al teach a method of treating a patient having glioblastoma comprising administering a fusion toxin wherein said fusion toxin comprises a mutant diphtheria toxin as taught by Greenfield et al fused to transferrin. Oldfield et al do not teach a method for treating a patient having glioblastoma comprising administering a fusion toxin wherein said fusion toxin comprises a mutant diphtheria toxin fused to urokinase plasminogen activator.

Mori et al teach that urokinase-type plasminogen activator receptor is unregulated in glioma cells exhibiting enhanced invasion activity such as in glioblastoma multiforme (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the amino terminal fragment of urokinase plasminogen activator for transferrin in the method of treating as taught by Oldfield et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rajagopal et al on the representative number of urokinase plasminogen receptors on glioblastoma cell lines which range from 670 sites/cell to 10^6 sites/cell (page 7570, Table II) and the teachings of Mori et al on the up regulation of urokinase type plasminogen activator receptor in glioblastoma multiforme. Thus, one of skill in the art would be motivated to target

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the plasminogen activator receptor because glioblastoma cells would be expected to express numerous receptor molecules.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

June 2, 2003